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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,686	02/14/2002	James G. Boyd	PC23001A	2658

23913 7590 12/02/2004

PFIZER INC
150 EAST 42ND STREET
5TH FLOOR - STOP 49
NEW YORK, NY 10017-5612

EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,686	BOYD ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. With respect to (1), the nature of the invention is a compound to be used in treating Alzheimer's disease, Crutzfield-Jacob's disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, Down's syndrome, pancreatitis, inclusion body myocitis, other peripheral amyloidoses and diabetes in a mammal. With respect to (2), there is no effective palliative or preventive treatment for the inevitable neurodegeneration of Alzheimer's disease (see the WO Patent Application 01/00665, page 1, second paragraph). No compound has been developed that significantly affects the course of Alzheimer's disease (see the Potter et al article, Nature Biotechnology, Vol. 18, page 125, column 1, first paragraph). Memapsin 2/BACE-1 is a "potential" target for inhibitor drugs against Alzheimer's diseases (see

the Hong et al article, Science, Vol. 290, especially page 150, column 3), but there is no indication that this disease is a potential target for inhibitor drugs against any other disorder or condition claimed by Applicants. There is no compound of similar structure which has been used to treat any of the disorders or conditions claimed by Applicants. With respect to (3), the relative skill of those in the art is high. With respect to (4), the art is not able to predict whether a compound can be used to treat the diseases mentioned in (1) above in the absence of any experimental testing. As indicated by the Potter et al article (Nature Biotechnology, Vol. 18, page 126, column 2, last paragraph, through column 3), the mere in vitro identification of an inhibitor to BACE does not in and of itself establish that the inhibitor can be used in vivo to treat Alzheimer's disease. With respect to (5), the claims are relatively broad with respect to the diseases to be treated. The diseases to be treated, with the exception of Alzheimer's disease, are not caused by the enzyme which is to be inhibited by the claimed compound. There is no common biochemical mechanism which underlies the claimed disorders or conditions such that a treatment useful for treating one condition or disorder would have been expected to be useful in treating the other conditions or disorders. With respect to (6), no direction or guidance has been presented as to how the claimed compound can be used to treat Alzheimer's disease in vivo (see the Potter et al article discussed above) or as to how an enzyme inhibitor can be used to treat disorders or conditions which do not involve the enzyme which is to be inhibited by the compound. For example, the Vassar et al article (Science, Vol. 286, page 739, column 2, last paragraph) teaches that BACE is expressed at higher levels in neurons than in glia. The specification does not disclose how BACE inhibitors can be used to treat disorders or conditions which do not involve neurons which are expressing BACE, e.g., in the treatment of prion

disorders, head trauma, Down's syndrome, and diabetes. With respect to (7), there are no working examples in the application, in vitro or in vivo or otherwise, which show that the claimed compound has any activity. There is a single statement, at page 10, lines 19-20, of the specification, that the claimed compound binds to the enzyme with an IC_{50} equal to $49x10^{-9}M$ as measured by an in-vitro ELISA assay. However, there is no discussion as to how this assay was performed, and in the absence of details of the experimental procedure involved, it is not possible to conclude that the assay is reasonably predictive of in vivo success. With respect to (8), the quantity of experimentation necessary in order to use the invention would be vast, given the lack of any experimentation provided in the specification, given the wide range of disorders and conditions which are to be treated in the claimed invention, and given the current lack of success in treating Alzheimer's disease. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

3. Applicant's arguments filed March 21, 2004 have been fully considered but they are not persuasive.

The examiner maintains his position for the reasons of record. The examiner agrees with Applicants' summary of the case law at page 3, first full paragraph, and page 6, first full paragraph, of the response. Applicants' rejection is consistent with the case law as summarized by Applicants. The examiner will respond to Applicants' analysis of the factors in the order presented in Applicants' remarks:

With respect to the first factor, the claimed invention is relatively narrow with respect to the compound recited in the claims, but is relatively broad with respect to the range of the

disorders or conditions to be treated. The range of disorders or conditions to be treated is considered to be relatively broad because there is no common biochemical mechanism which underlies the claimed disorders or conditions such that a treatment useful for treating one condition or disorder would have been expected to be useful in treating the other conditions or disorders.

With respect to the second factor, Applicants contend that there is relevant prior art that needs to be taken into account when evaluating the state of the prior art, and cite to WO 01/00665 and the Hong et al article. However, these references have been taken into account and discussed in the above rejection, the Applicants and the examiner drawing different conclusions from their disclosures. It is noted in their rebuttal that Applicants do not discuss any prior art relevant to the other diseases or disorders recited in Applicants' claims and not involving beta amyloid, i.e. Crutzfield-Jacob's disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, Down's syndrome, pancreatitis, inclusion body myocitis, other peripheral amyloidoses and diabetes.

Applicants contend that the WO 01/00665 (published on January 4, 2001, filed on June 27, 2000) and the Potter et al article (published in February 2000) were published prior to the filing date of the present and that the compound of the present invention was unknown to these references. However, the dates of these references are sufficiently close to Applicants' provisional filing date of February 20, 2001 and to Applicants' non-provisional filing date of February 14, 2004 to constitute evidence of the state of the art at the time Applicants' invention was made, especially in the absence of any intervening reference which shows a change in the state of the art. The implication from Applicants' comment that Applicants' compound was

unknown to these references is that if a compound is novel and unobvious over the prior art, then the compound is enabled because the prior art will not have been able to consider the utility of the compound. This argument is not supported by the law - enablement is a requirement which is separate from novel and nonobviousness.

With respect to the third factor, the examiner agrees that a person of ordinary skill in the art at least has a Ph.D.

With respect to the fourth factor, because Potter et al article is a published article in a relevant scientific magazine, it constitutes evidence which may be relied upon in support of a rejection for lack of enablement. Applicants have not cited any evidence or reference which supports the proposition that one skilled in the art could predict whether a compound can be used to treat the claimed diseases and disorders in the absence of any experimental testing.

With respect to the fifth factor, the range of disorders or conditions to be treated is considered to be relatively broad because there is no common biochemical mechanism which underlies the claimed disorders or conditions such that a treatment useful for treating one condition or disorder would have been expected to be useful in treating the other conditions or disorders. Applicants point out that the examiner has not cited to any paper or publication or other evidence which establishes that the claimed diseases and disorders, with the exception of Alzheimer's disease, are not caused by the enzyme which is to be inhibited by the claimed compound. The examiner agrees - he can not find any evidence which shows any connection between BACE or beta amyloid deposition and Crutzfield-Jacob's disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, Down's syndrome, pancreatitis, inclusion body myocitis, other peripheral amyloidoses and diabetes.

These diseases and disorders have causes and symptoms which are recognized by those skilled in the art not to involve BACE or beta amyloid deposition. In the absence of evidence of such a connection, and in the absence of actual experimental evidence which shows that the claimed compounds can be used to treat the claimed diseases and disorders, one skilled in the art would not expect to be able to practice the claimed invention. It should be noted that reasoning can be used as an alternative to objective evidence of nonutility to show that an invention is not enabled. See Ex parte Sudilovsky, 21 USPQ2d 1702 (BPAI 1992), and in Applicants' quotation from Marzocchi, note the words "or reasoning".

With respect to Applicants' discussion of page 10, lines 15-22, of the specification, this part of the specification is discussed in the enablement rejection in the discussion of factor (7). There is no discussion in the specification as to how this assay was performed, and in the absence of details of the experimental procedure involved, it is not possible to conclude that the assay is reasonably predictive of in vivo success, especially in view of the teachings of the Potter et al article (Nature Biotechnology, Vol. 18, page 126, column 2, last paragraph, through column 3) that the mere in vitro identification of an inhibitor to BACE does not in and of itself establish that the inhibitor can be used in vivo to treat Alzheimer's disease.

While the examiner agrees with the burden of evidence set forth at page 7, lines 5-7, of the response, the examiner maintains that he has met this burden through the citation and discussion of the WO Patent Application 01/00665, the Potter et al article, and the Vassar et al article, and by the provision of scientific reasoning. The examiner agrees with Applicants' discussion of the legal requirements for working examples at page 7, lines 17-20; however, the instant claimed invention is not deemed to be otherwise disclosed in such a manner that one of

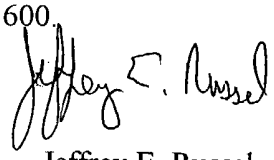
ordinary skill in the art is able to practice it without an undue amount of experimentation. The discussion of how to prepare the compounds, and the standard specification language concerning how the compounds can be administered to a patient, do not address the issue of how an enzyme inhibitor can be used to treat diseases or disorders which do not involve the enzyme, or of how an enzyme inhibitor can be used to treat Alzheimer's disease in the absence of any supportive experimental evidence.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (703) 872-9306; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

November 23, 2004